dial infarction, stroke, and tissue or organ necrosis from ischemia or venous congestion. More overall attention has been directed at prevention of arterial occlusion and loss of perfusion, although tissue injury due to venous thrombosis can be as destructive and is in some situations more common than arterial obstruction.

Thrombosis occurs through the interaction of blood elements with tissue factor and subendothelial components of injured or altered blood vessel walls [3]. Stasis of blood flow enhances this interaction. Platelet aggregation and activation of the coagulation system lead to thrombus formation. In addition, platelet activation and endothelial and smooth muscle cell disruption result in release of a number of mitogens, growth-promoting factors, and cytokines [4]. Potent mitogens, such as fibroblast growth factor and platelet-derived growth factor, contribute to reendothelialization by stimulating smooth muscle cells, fibroblasts, endothelial cells and inflammatory cells to migrate and replicate [5]. Smooth muscle cells also undergo phenotypic transformation to the synthetic subtype, and they secrete extracellular collagen and proteoglycan matrix that produces fibrocellular intimal thickening and luminal narrowing [6]. Both thrombosis and intimal hyperplasia are instrumental in the development of restenosis.

Many experimental models of restenosis have been studied. All have been limited by the impossibility of recreating the lesions of human atherosclerosis and coronary artery disease in other mammals. However, the characterization of the arterial 'response to injury' by many investigators [7,8] has paved the way for a logical approach to pharmacologic prevention of restenosis in humans. By continuing to study and characterize restenosis in animal models, a better understanding of human restenosis and its prevention can be achieved.

Many pharmacologic agents have been tested in an effort to reduce thrombosis and restenosis. Promising results from animal studies have thus far been disappointing in subsequent human clinical trials [9]. Systemic drugs that have been examined include anti-platelet agents, anti-thrombotic agents, anti-inflammatory agents, antiproliferative agents, vasodilators, smooth muscle cell growth inhibitors, and lipid-lowering agents. The lack of success with any of these agents may in part be due to systemic toxicity in the face of inadequate local drug levels capable of inducing the desired effects at the site of disease. These failures of systemic therapy have led to a widespread recent interest in local drug delivery systems.

1.2. Biodegradable local drug delivery systems

A variety of local drug delivery strategies are discussed within this issue. A general advantage of implanted controlled-release polymer systems over systemic therapies is the potential for delivery of high local levels of drug with lowered systemic exposure and toxicity [10]. In particular, local delivery of antithrombotic agents avoids the hemorrhagic complications of systemic administration. *Controlled release* refers to the use of polymeric materials within which drugs are stored in reservoirs or integrated into the polymer matrices to allow sustained delivery of the drugs [11]. In vitro and in vivo assays of drug release and biological activity are part of the evaluation of any polymer-drug system. Biodegradable controlled-release systems offer the advantage of gradual biological elimination without a residual implant structure remaining. Biodegradable polymers, also called bioerodible or bioabsorbable polymers, are synthetic or natural polymers which hydrolyze in vivo [12]. A large selection of biodegradable polymers are available as carriers for local drug delivery [13,14]. Examples of these polymers are shown in Table 1. These polymers degrade in the body at various time periods, from a few days up to 2–3 years. These polymers degrade into nontoxic acids or alcohols that are readily excreted from the body. The in vivo elimination time is determined by the nature of the polymer chemical linkage, the solubility of the degradation products, the size, shape and density of the device, the drug and additive content, the molecular weight of the polymer, and the implantation site. Many of the site-specific applications of drugs are for periods of several weeks, requiring polymer carriers that degrade and are eliminated from the body soon after. It is believed that for many of the applications the polymer should be eliminated within 6 months after implantation. From the available polymers, polyanhydrides, collagen and copolymers of lactide and glycolide are useful for short-term drug release and device elimination in vivo [12]. There are three general mechanisms of polymer hydrolysis [15]:

Table 1
Common biodegradable polymer carriers

Polymer	Polymer linkage	Principal degradation product	Elimination time[a] (months)
Poly(lactic acid)	–CO–O–	Lactic acid	12–24
Poly(lactic-*co*-glycolic acid)	–CO–O–	Lactic and glycolic acid	6–12
Poly(glycolic acid)	–CO–O–	Glycolic acid	2–4
Poly(caprolactone)	–CO–O–	Hydroypentanoic acid	18–24
Poly(hydroxybutyrate)	–CO–O–	Hydroxybutyric acid	18–24
Poly(orthoester)	–CO–O–	Alcohols	12–24
Poly(alkane anhydride)	–CO–O–CO–	Aliphatic diacids	0.2–4
Gelatin, collagen	–CO–NH–	Amino acids	0.2–1
Oxidized cellulose	–C–O–CH–O–	Alcohols, CO_2	0.2–1
Poly(phosphazene)	–N=P–	Phosphates, ammonia	6–18

[a]Elimination times vary depending on implant size and shape, density, implantation site and molecular weight (taken from ref. [12], p. 22).

1. Erosion of cross-linked polymers with hydrolytically unstable cross-links. Polymer chains are freed from the bulk matrix as the cross-links are hydrolyzed. This mechanism is useful for drugs with low water-solubility or large macromolecules.
2. Solubilization of water-insoluble polymers by hydrolysis, ionization or protonation of a side group, without any significant change in polymer molecular weight. This mechanism is mainly used in topical or oral applications.
3. Erosion of water-insoluble polymers with labile backbone bonds. Hydrolysis of the polymer backbone produces low molecular weight, water-soluble molecules. This mechanism is most useful for systemic administration of drugs from subcutaneous, intramuscular or intraperitoneal implantation sites.

Bioerodible polymers can be reservoir or matrix devices. In a reservoir system, a core of drug is surrounded by a polymer and the rate-limiting step in drug release is the diffusion of drug outward through the polymer. This rate can be controlled or adjusted by changing the nature of the bioerodible membrane.

In a matrix system, drug is dispersed uniformly throughout a solid polymer. Drug release is a product of either diffusion through or erosion of the polymer.

In order to be clinically useful, biodegradable polymers must also be biocompatible. The polymer and its degradation products must either be safely eliminated from the body or metabolized to nontoxic substances.

There are many natural and synthetic polymers that have potential application as biodegradable drug delivery systems. These include polyamides, polyesters, polyanhydrides, poly(orthoesters), and various polysaccharides. Examples of these biodegradable polymers that have been used to inhibit thrombosis and restenosis will be discussed in the remainder of this article.

2. Biodegradable devices for prevention of restenosis

2.1. Perivascular therapy

The efficacy of heparin in venous thromboembolism was established by Barritt and Jordan in 1960 [16]. Since then heparin has been used widely as an anticoagulant and antiplatelet agent. Heparin binds to and accelerates the action of antithrombin III, thus neutralizing the serine protease clotting factors (XII, XI, IX, X). Heparin also directly inhibits individual clotting factors, such as Xa, at concentrations significantly lower than those at which interaction with antithrombin III takes place [17]. In addition heparin reduces platelet adhesiveness [18], binds to components of damaged vascular walls [19–21], and directly inhibits smooth muscle cell proliferation and migration [22,23], thereby inhibiting thrombosis and stenosis.

Okada et al. were the first to evaluate perivascular heparin delivery from a biodegradable polymer as a method of inhibiting thrombosis and neointimal fibrosis [24,25]. Polyvinyl alcohol (PVA), a water-soluble, nontoxic polysaccharide was loaded with heparin and applied to the adventitia of rat carotid arteries that had undergone balloon catheter endo-

thelial injury. Subsequent arterial occlusion for 1 h with microclamps contributed additional circulatory stasis. Vessels treated with heparin/PVA had significantly reduced thrombus formation compared to vessels treated with PVA alone. Similar studies of injured rat carotid arteries injured by the balloon catheter technique that were treated with PVA/heparin or PVA alone revealed a significant reduction in intimal cross-sectional area at 5, 10 and 20 days after surgery in heparin/PVA-treated vessels compared to control vessels. In both experiments, systemic anticoagulation was avoided as confirmed by measurement of prothrombin time and partial thromboplastin time. Delivery of heparin from PVA to the adventitia at the site of vessel injury inhibited thrombosis and smooth muscle proliferation through specific local effects.

To determine the release kinetics and distribution of heparin from perivascular PVA, the same investigators used tritiated heparin [26]. Labeled heparin was found in the vessel walls and especially within smooth muscle cell nuclei at all time periods after injury as measured by autoradiography.

Jones et al. studied the effects of locally-released heparin from PVA in rat microvascular anastomes [27]. The arterial inversion graft thrombosis model was employed, and perivascular PVA/heparin was compared to perivascular PVA alone or systemic heparin. Vessel patency rates were significantly higher in the PVA/heparin and systemic heparin groups compared to controls. However, local hematoma formation was prohibitive.

In each of the above studies using PVA heparin, a silastic shell was needed to contain the semi-liquid PVA-heparin or PVA alone in the perivascular position. This requirement detracted from the advantages of the otherwise biodegradable drug delivery system. In subsequent studies, Orloff et al. applied perivascular heparin released from a biodegradable polyanhydride to microvascular anastomoses [28]. This polymer, poly(dimer erucic acid-*co*-sebacic acid) (P(FAD-SA)), offered the advantage of a solid matrix that could be placed in strips around the site of microvenous inversion grafts in the rat. In this study, vessel patency rates were significantly greater in polyanhydride-heparin-treated vessels compared to controls at 24 h and 7 days after surgery. Measurement of partial thromboplastin time confirmed an absence of systemic anticoagulation, and no complications (such as hematoma or inflammation) occurred.

Thin flexible sheets composed of laminated (P(FAD-SA)), poly(lactic acid) (PLA) loaded with heparin were evaluated in vitro and in vivo [29]. PLA was used for coating the polyanhydride to improve the release profile and improve the strength of the films. Heparin was released constantly for 20 days from laminates of 2% loaded polymer I coated with drug free polymer II. The uncoated film of polymer I released heparin for only 4 days.

A study was conducted to determine the potential interaction between heparin and degradable polyanhydrides and polyesters. Samples of polymers were placed in solutions of heparin and the heparin concentration was determined (Azure A method) as a function of time for 24 h. As control, heparin solution without polymer was used. No change in heparin concentrations was found at all time points and at all concentrations. No nitrogen was found in the polymer samples. In addition, heparin was completely isolated from the polymer by extraction and in vitro release. These results confirm that there is no chemical interaction between heparin and the polymer carrier.

The localized delivery of heparin to the carotid implant site was investigated by implanting polymer loaded with [^{3}H]heparin around the carotid artery of rats and the heparin release and tissue distribution was monitored. The maximum heparin concentration in the artery exposed to the drug was 3–4 days for the P(FAD-SA) uncoated device (fast releasing system) and 11 days for the coated devices. The control artery, the uncovered segments of the artery, and the surrounding tissue contained negligible amounts of radioactivity. These data confirm that heparin was delivered locally without systemic exposure.

Two independent animal studies were conducted to evaluate the effectiveness of these heparin releasing devices. In both studies the balloon catheter injury in a rat model was used. After inflicting an injury to the common carotid, a matrix oriented with its long axis along the artery was placed under the injured portion of the vessel (Fig. 1). Two groups of rats (7 each) were implanted with zero or 2% heparin sodium loaded poly(FAD-SA)1:1 coated with PLA. The rats were sacrificed after 21 days and the carotid arteries were isolated and evaluated. In both studies

Fig. 1. Heparin releasing polymeric sheet placed along the injured portion of the common carotid artery of a rat.

the control group showed a significant reduction of the artery internal diameter with SMC neointima ratio greater than 1. The treated rats showed a very thin layer of neointima.

Simons and colleagues reported the periadventitial delivery of antisense c-*myb* oligonucleotide from a biodegradable pluronic gel to rat carotid arteries injured by balloon angioplasty in order to suppress intimal accumulation of smooth muscle cells [30]. Antisense oligonucleotide suppresses the increase in c-*myb* messenger RNA levels that is seen in mitogen-induced proliferation of vascular smooth muscle cells, thereby halting cell proliferation. In this study, the pluronic gel carrier disappeared over 1–2 h. This study constitutes one of the first uses of antisense oligonucleotide to inhibit a specific gene product that has a subsequent effect on a cellular process, namely intimal smooth muscle cell accumulation. In another experiment, antisense oligonucleotide, c-*myc* phosphothiorate deoxyoligonucleotide, was incorporated along with an antiproliferative agent, pentosan, into the biodegradable plastic poly-L-lactide [31]. In vitro assays demonstrated sustained release of biologically active compounds. Preliminary in vivo studies using this polymer wrapped around a stent that was implanted in porcine coronary arteries demonstrated antiproliferative activity toward vascular smooth muscle cells. In a recent study [32], sought to confirm and extend the hypothesis that antisense to c-*myb* results in a specific antiproliferative effect, a comprehensive assessment was conducted by using different oligonucleotide preparations, different species, and tissue and cellular uptake experiments. The researchers concluded that there is a potential nonspecificity and lack of consistency of the antisense oligonucleotide to c-*myb* in vitro and in vivo.

2.2. *Intravascular therapy*

One of the first reports of a biodegradable intravascular stent was made by Bier and colleagues [33], who performed in vitro tests of a stent made of Type I collagen polymer. No drug was delivered from the collagen polymer, but the stent was found to conform completely to porcine artery walls in 17 of 19 insertions. This device represents a potential intraluminal site of controlled drug release, similar to drug coating and drug release from non biodegradable stents described elsewhere in this issue.

2.3. Epicardial therapy

Non biodegradable cardiac controlled-release devices have been used previously in the clinical setting to prevent pacer lead threshold elevation [34], and experimentally to inhibit arrhythmias [35], endocarditis [36], and calcification [37]. More recently, epicardial placement of cyclosporine-containing collagen was placed around cardiac homografts at the time of rat heterotopic heart transplantation [38]. Significant graft survival advantages were noted in both low- and high- dose (0.2 or 1 mg/kg/day released) treatment groups with this immunosuppressive drug compared to controls, and very high cardiac tissue levels of cyclosporine (CyA) were achieved with clinically negligible blood CyA levels and very low kidney CyA levels. While this device is not directed at preventing stenosis or thrombosis, it does represent another example of controlled drug delivery from a biodegradable polymer to achieve high local tissue levels of drug in the region of the coronary arteries without systemic toxicity.

3. Conclusions

The ideal device that consistently aids in the prevention of vascular thrombosis and restenosis remains to be identified. The move from the use of systemic therapy towards local delivery of pharmacological agents represents a new level of specificity in the treatment of conditions such as coronary artery disease, and parallels an improved understanding of the pathophysiology of such diseases. A reduction in systemic side effects has already been realized with the use of a wide variety of local drug-polymer delivery systems. Furthermore, biodegradable implant systems have the potential for atraumatic local delivery of antithrombotic and antistenotic agents without the associated risks of permanent alloplastic or nonabsorbable implants. Despite the fact that no animal or in vitro model perfectly mimics the human atherosclerotic disease process, continued study in such experimental models holds promise for identification of the ideal combination of polymeric delivery vehicle and pharmacologic agent to assure vascular patency.

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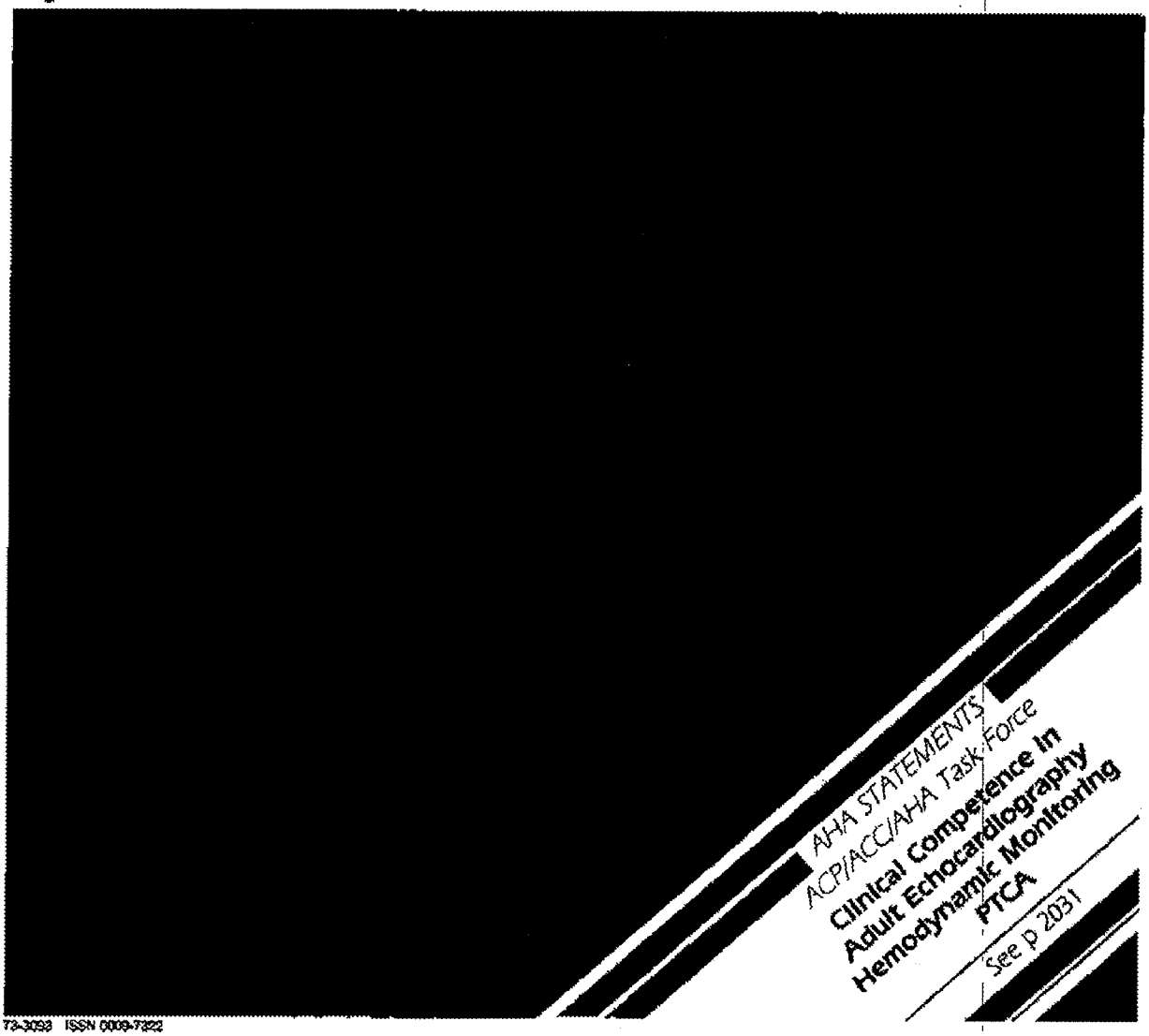

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A Controlled Trial of Corticosteroids to Prevent Restenosis After Coronary Angioplasty

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A multicenter, double-blind, placebo-controlled trial was conducted to determine if corticosteroids influence the development of restenosis after successful percutaneous transluminal coronary angioplasty (PTCA). Either placebo or 1.0 g methylprednisolone (steroid) was infused intravenously 2–24 hours before planned PTCA in 915 patients. The PTCA patient success rate was 87% (mean) in the eight centers. There were no differences in clinical or angiographic baseline variables between the two groups. End-point analysis (angiographic restenosis, death, recurrent ischemia necessitating early restudy, and coronary artery bypass graft surgery) showed that there was no significant difference comparing placebo- with steroid-treated patients. Angiographic restudy showed the lesion restenosis rate to be 39% (120 of 307 lesions) after placebo and 40% (117 of 291) after steroid treatment (p=NS). We conclude that pulse steroid pretreatment does not influence the overall restenosis rate after successful PTCA. (*Circulation* 1990;81:1753–1761)

Successful treatment of patients with stenotic coronary arteries by percutaneous transluminal coronary angioplasty (PTCA) is associated with restenosis in approximately 25–55% of cases.[1–3] Despite advances in techniques, the occurrence of restenosis does not seem to have been altered. This is, in part, related to the fact that although the primary cause of restenosis must be associated with the vascular response to balloon-induced injury, the exact mechanisms have not been identified.

Restenosis is believed to be a multifactorial process involving certain clinical, anatomic, and procedural factors.[3] Balloon-induced vascular injury damages the endothelium and deeper plaque structures, so within several days, inflammatory cells are present.[4] Recurrent narrowing can be identified angiographically at certain sites approximately 12 weeks after PTCA.[5] This process probably involves the vessel wall and blood elements, as well as factors that influence cellular proliferation.[3,6–9] One natural model for coronary artery plaque injury may be found in patients dying after hospitalization for unstable angina. Mononuclear cells and edematous changes have been found in the subendothelium of proximal coronary arteries, with edematous changes at sites of naturally occurring plaque injury.[10] These mononuclear cells are transformed from monocytes to macrophage types and later to foam cells.[10] Other studies have suggested that endothelial damage, caused by migration of blood-borne mononuclear cells, may be an early change of atherosclerosis.[11] These mononuclear cells are known to release vasoactive substances that influence platelet aggregation, other leukocyte properties, and proliferation of exposed vascular smooth muscle.

The effects of corticosteroids on mononuclear cells are well known.[12] Some animal studies have shown that corticosteroids may modify induced athero-

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*Multi-Hospital Eastern Atlantic Restenosis Trial (M-HEART) group participants are listed in the "Appendix."

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sclerosis.[13-17] Results of a small study in humans, in which corticosteroids were used to control restenosis, were interpreted as suggesting a beneficial trend, but a larger sample was required to reach more definitive conclusions.[18] Accordingly, we conducted a large, prospective, multicenter, double-blind, placebo-controlled trial to evaluate the role of corticosteroids in reducing the rate of restenosis in patients after successful PTCA and also to identify factors predictive of restenosis.[19]

Methods

Patient Selection

During a 19-month period, 915 patients were enrolled from eight centers (see "Appendix"). All patients presenting for PTCA and who had at least one eligible stenosis (see definitions) were considered candidates. Patients undergoing PTCA for the specific purpose of revascularizing acute myocardial infarction, as well as those with left main coronary artery stenosis (≥50% luminal diameter reduction), contraindication to steroid use, anticipated need for corticosteroids or other immunosuppressive agents, renal failure, and those receiving corticosteroids within the preceding 30 days were specifically excluded. The study protocol was approved by institutional review boards at each center.

Study Design (Figure 1)

Drug assignment and administration. After eligibility was evaluated, the patients gave written informed consent, which included intention to undergo angiographic restudy at 6 months, and they were randomly assigned to either a placebo or a methylprednisolone group. In double-blind fashion, either 1 g methylprednisolone in 200 cc of 5% dextrose and water, or 200 cc of 5% dextrose and water alone was given by venous infusion during a 30–45 minute interval, 2–24 hours before the planned PTCA. Patients also received their usual antianginal medications, which in most instances included nitrates in addition to a calcium antagonist and/or a β-adrenergic blocker.

Angioplasty procedure. Aspirin (325 mg orally) and heparin (10,000 units intravenously) were given before the PTCA procedure. Heparin was supplemented by an additional 1,000 units/hr during the procedure. Nitroglycerin was given intravenously just before the pre-PTCA (baseline) angiogram. This angiogram was filmed in a view revealing the stenosis in its maximum degree of narrowing. The PTCA was performed with standard balloons and guidewires.

After the procedure, aspirin was continued, but an attempt was made to withdraw antianginal drugs over several weeks, provided no other indication (e.g., hypertension, arrhythmia, or recurrent ischemia) for the drugs existed. Patients with successful PTCA (see below) were followed up and after 6±2 months, were scheduled for restudy. The restudy angiogram was filmed after nitroglycerin in the same projection used for the baseline angiogram. Follow-up was terminated either after an early end point had been attained or the restudy angiogram had been performed.

Definitions

Eligible stenosis. For a patient to qualify for entry into the study, PTCA had to be performed on at least one stenosis with a 60% or greater luminal diameter reduction within 2–24 hours of completion of study drug infusion. The screening percent diameter stenosis on the baseline angiogram was determined as the greatest diameter reduction observed in the "worst" single view. This "optimal" view was recorded. Initial visual assessment required confirmation by caliper measurement of the site of maximal narrowing and adjacent noninvolved segment from the baseline angiogram, recorded just before PTCA. From the optimal view, a frame near end diastole, when artery motion blurring, lesion foreshortening, and overlapping were minimal, was selected for measurement. The PTCA result was considered successful when a diameter stenosis of less than 50% was observed after the dilation by the angiographic technique noted above. The restudy angiogram was repeated with the same worst view recorded at baseline. Physicians who performed the angiograms both initially and at restudy, those who made the caliper measurements, and those who followed up the patients were blinded as to therapy.

End points. The following end points were prospectively defined. Angiographically documented restenosis was the primary end point. Restenosis was defined as a diameter stenosis of at least 50% measured on the restudy angiogram by the same technique outlined for the baseline angiogram. The patient was considered to have reached an early end point before the protocol-directed restudy (6±2 months) when recurrent chest pain or ischemia, occurring before 4 months after PTCA, necessitated a repeat coronary angiogram that showed no restenosis, and a 6-month restudy was not available (Figure 1). Other early end points included acute myocardial infarction, need for coronary artery bypass surgery, and death. All patients with an early end point were assumed to have restenosis for the intention-to-treat analysis. Since the primary dilated lesion has clinical relevance, it was used in the analysis of patient restenosis rate, and all dilated lesions were used in the analysis of lesion restenosis rate.

Statistical Analysis

Sample size considerations. We assumed that the restenosis rate would be approximately 20% at 6 months (best case), and that a 50% reduction would be necessary to justify, for ethical and clinical reasons, a pharmacotherapeutic intervention to prevent restenosis. Thus, a truly effective approach would be associated with a restenosis rate of approximately 10%. A two-armed trial would require approximately 300 patients (assuming at least one lesion per patient) in each arm to provide adequate conclusions with an α or Type I error of 0.05 and a β or Type II

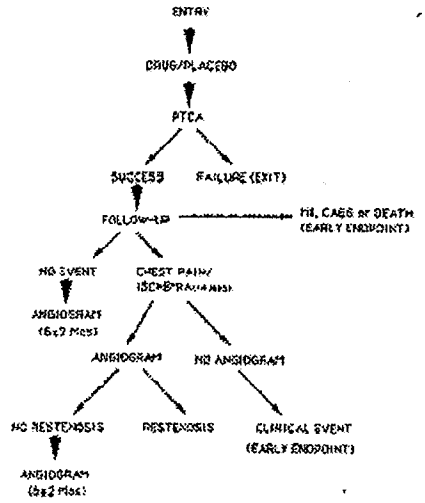

FIGURE 1. *Flow chart of study design. PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; CABG, coronary artery bypass grafting.*

error of 0.90 by a two-tailed test. A sample of this size would also provide sufficient numbers for analysis of factors relating to restenosis. Assuming an immediate success rate for PTCA of 80% at our centers (worst case) and assuming that approximately 25% of patients would be unavailable for angiographic restudy, we determined that a sample size of approximately 1,000 patients would be required (assuming one lesion per patient). This sample size would be expected to provide the required 800 successfully dilated patients eligible for follow-up, further yielding approximately 600 patients available for final angiographic analysis.

Data collection and analysis. Data were collected on standardized forms and sent to the Data Coordinating Center. Reports relative to enrollment and restudy rates, as well as dates for individual patient restudy, were sent to each center on a monthly basis. For quantitative data, unpaired *t* tests were used, and for qualitative data, χ^2 analyses were performed. All tests were two-tailed and were completed with the SAS statistical software package (Statistical Analysis Systems, Inc., Cary, North Carolina). The analyses were performed using the first or primary dilated lesion and also using all dilated lesions.

To better characterize the restenosis process and the possible effect of methylprednisolone, we prospectively chose to examine the influence of a number of patient- and lesion-related characteristics.[20,21] It was also recognized that the balloon-induced injury produced in certain lesions might not be extensive enough to be modified by methylprednisolone. Thus, we chose to examine the effect on lesions according to their risk for development of restenosis. We performed this examination retrospectively, using the hypothesis that methylprednisolone would be effective in attenuating restenosis in patients identified as being at high risk for restenosis. The four continuous variables that showed statistically significant differences between lesions that were and those that were not restenosed were used to classify lesions into low-, high-, and intermediate-risk groups for restenosis as follows. Lesions in the worst three quartiles of three of four of these factors were assigned a high-risk rank, and those in the best three quartiles of three of four factors were assigned a low-risk rank for restenosis. The remaining lesions were assigned to the intermediate-risk group. Since restenosis risk probably represents a multifactorial process, this hypothesis was also tested by multiple stepwise logistic regression analysis, with an α to enter of p less than 0.10 and an α to remove of p more than 0.10, with the risk of restenosis as the dependent variable. The α represents the probability that the variable makes an independent contribution to the explanatory power of the model. Restenosis rates in placebo and methylprednisolone groups were then examined as a function of restenosis risk, and appropriate corrections were made for multiple comparisons.

A random sample of 100 patient studies (two films, one pre-PTCA and one restudy angiogram from each of 50 patients) was submitted to the Quantitative Coronary Angiography (QCA) Laboratory. Comparison of caliper measurements of stenosis severity (percent diameter reduction) made at all eight centers was performed at the QCA by a computer-based analysis of stenosis geometry.[22] Correlation between the two methods gave an $r=0.891$, $y=0.945x+1.621$ ($p<0.001$). Additionally, on-site caliper measurements were compared with those made by a panel of three expert angiographers not involved in the study who were blinded to treatment. No significant differences were noted between on-site measurements and those made by either the computer-based QCA analysis or the panel.

Results

Of the 915 patients enrolled in the study, 457 were randomized to receive methylprednisolone and 458 to receive placebo (Figure 2). Forty-eight patients in the methylprednisolone group and 41 in the placebo group were excluded. Thirty-four patients in the methylprednisolone group and 22 in the placebo group were excluded because they did not have PTCA performed within 24 hours of the study drug infusion. This event occurred either because planned surgical backup could not be obtained or the coronary anatomy had changed between the referring angiogram and the baseline angiogram completed just before planned PTCA. In the latter situation, the investigator no longer believed that PTCA was the most appropriate intervention. Included in this category were cases in which the disease had progressed, as well as cases in which a stenosis of more than 60% could not be identified after nitroglycerin administration, and the previously identified stenosis was assumed to represent spasm. Thirty-three patients

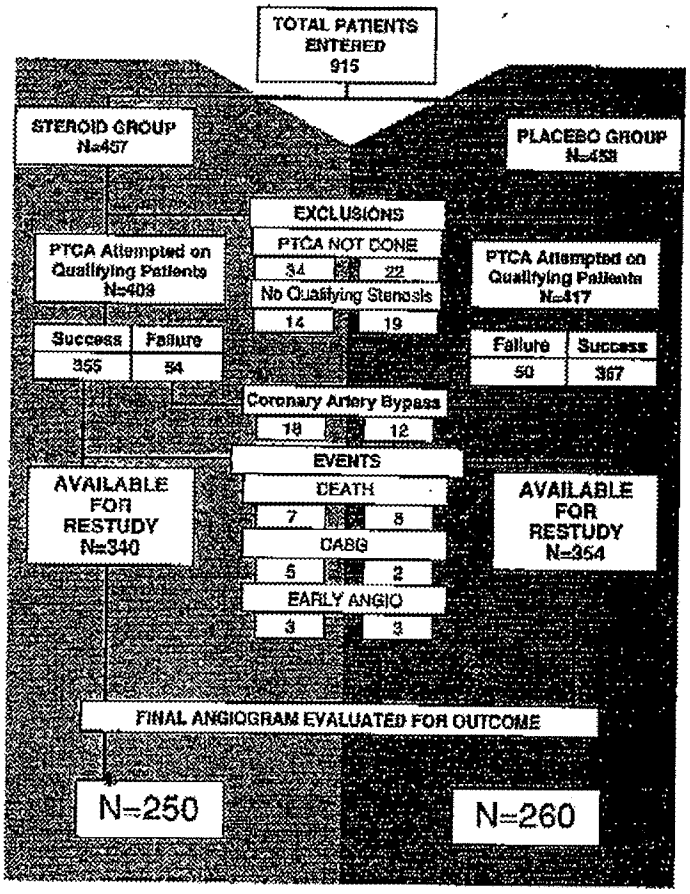

FIGURE 2. *Patient flow chart. PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; ANGIO, angiogram.*

(14 in the methylprednisolone group and 19 in the placebo group) who underwent PTCA were excluded because no qualifying stenosis could be identified when the baseline angiograms were later quantified by caliper measurement. Therefore, 409 eligible patients in the methylprednisolone group and 417 in the placebo group qualified for inclusion in the study.

Successful dilation occurred in 722 patients, and 75% of these had a result that was considered optimal, with a stenosis of less than 30% after PTCA. Successful dilation resulted in 355 patients randomized to methylprednisolone and 367 patients randomized to placebo (Figure 2). There were no significant differences in either clinical or angiographic characteristics comparing treatment groups at baseline (Table 1). Ninety-three patients in the methylprednisolone group and 100 in the placebo group had multiple vessels dilated. This difference was not statistically significant. There were no differences in success rates comparing the two treatment groups. Success rates for the 722 patients were uniform for all eight centers (mean, 87%), and the number of patients entered into the study by center ranged from 50 to 124. No significant difference in the number of patients requiring emergency coronary artery bypass surgery (5% in the methylprednisolone group and 3% in the placebo group) was found. During follow-up of the 722 successfully dilated patients, 28 patients had events that met the study criteria for early end points. Event distribution between the two study groups appears in Figure 2. Of these, 15 died, seven underwent coronary artery bypass surgery, and six had signs and/or symptoms suggesting early (<4 months) recurrent ischemia but were found not to have restenosis on restudy and did not undergo repeat restudy. Thus, 340 patients randomized to methylprednisolone and 354 randomized to placebo were available for restudy. A final angiogram was evaluated for outcome in 250 patients randomized to methylprednisolone and 260 randomized to placebo. Thus, the restudy rate was 73.5% of available patients, and comparison of those who were restudied with those who were not appears in Table 2. The only significant differences noted were with respect to age (2.2 years) and sex (7% more men), as fewer elderly women appeared in the restudied patients. In the 510 restudied patients, there were 598 dilated lesions, 291 in the methylprednisolone group and 307 in the placebo group, available for final angiographic analysis.

TABLE 1. Description of Treatment Groups

Characteristic	MP (*n*)	MP (%)	Placebo (*n*)	Placebo (%)	*p*
Patients (*n*)	355		367		...
Age (mean yr)	58.7		58.1		0.52
Men	283	(50.5)	278	(49.6)	0.20
Clinical findings					
Angina class (Canadian)					
I and II	92	(45.8)	109	(54.2)	0.25
III and IV	226	(52.0)	209	(48.1)	0.40
Angina duration (mean mo)	12.5	10.8		0.31	
Rest angina	189	(51.5)	178	(48.5)	...
Previous MI	84	(48.6)	89	(51.5)	0.85
Diabetes	47	(48.5)	50	(51.6)	0.94
Smoking (within 1 mo)	96	(49.7)	97	(50.3)	0.87
Nitrates	279	(50.6)	272	(49.4)	0.25
Calcium antagonists	293	(49.2)	303	(50.8)	0.61
β-Blockers	165	(50.5)	162	(49.5)	0.50
Angiographic findings					
Mean pre-PTCA stenosis (%)	82.64		82.72		0.92
Mean stenosis length (mm)	5.67		5.47		0.49
Lesion location					
LCA	176	(48.3)	187	(51.5)	0.60
LCx	79	(49.4)	81	(50.6)	0.85
RCA	86	(50.0)	86	(50.0)	1.00
Graft	11	(47.8)	12	(52.2)	0.84

MP, methylprednisolone; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; LCA, left coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

Overall, lesion restenosis rates were 40% (117 of 291) of lesions in the methylprednisolone group and 39% (120 of 307) of lesions in the placebo group ($p=0.78$). No significant difference occurred in the patient restenosis rates, as restenosis occurred in 43% (108 of 250) of patients after methylprednisolone administration and 43% (111/260) of patients after placebo administration. Likewise, the occurrence of restenosis, death, recurrent ischemia necessitating early restudy, and coronary artery bypass grafting in all qualifying patients was not significantly different comparing the methylprednisolone (34%, 141 of 409) and placebo (33%, 136 of 417) groups. There were no significant differences regardless of whether the analysis was done with all dilated lesions or only with the first or primary lesion dilated. Thus, to simplify presentation, the remainder of this section will focus on the analysis of all dilated lesions.

Univariate predictors of restenosis that were identified included stenosis location ($p<0.005$), baseline percent stenosis ($p<0.005$), stenosis length ($p<0.01$), diameter of the adjacent artery ($p<0.03$), and post-PTCA percent diameter ($p<0.01$). No differences were found comparing placebo group and methylprednisolone group restenosis rates according to stenosis location. Lesions falling within any three of the four lowest-risk quartiles (baseline percent stenosis ≤88%, stenosis length ≤7.0 mm, adjacent artery diameter ≥2.5 mm, and post-PTCA percent stenosis ≤30%) and any three of the four highest-risk quartiles (baseline percent stenosis ≥80%, stenosis length ≥4.8 mm, adjacent artery diameter ≤2.89 mm, and post-PTCA percent stenosis >22%) for each of the latter four predictors were ranked as low- and high-risk lesions, respectively. The remaining lesions were ranked as intermediate risk. A significant difference (corrected for multiple comparisons) in restenosis rates was found in the low-risk restenosis subset comparing methylprednisolone (20%, 15 of 75 lesions) and placebo (37%, 37 of 99 lesions; $p=0.013$) groups. No significant differences were found in either the intermediate- or high-risk restenosis subsets.

These same four covariates were also identified by multivariate analysis as important independent predictors of restenosis. The model using percent stenosis ($p<0.01$), stenosis length ($p<0.001$), adjacent artery diameter ($p<0.012$), and post-PTCA percent stenosis ($p<0.005$) was used to create subsets of lesions at deciles of increasing risk for restenosis (Figure 3). Again, the lesions at lowest risk for restenosis showed a trend toward a reduced observed restenosis rate, comparing methylprednisolone and placebo groups. Thus, for the majority of lesions (55%, 331 of 598) in the lowest-risk categories defined by multivariate analyses, there was a trend, not statistically significant, toward a reduced restenosis rate after methylprednisolone administration.

TABLE 2. Description of Patients Restudied and Those Not Restudied

Characteristics	Patients restudied (n)	(%)	Patients not restudied (n)	(%)	p
Patients (n)	510		184		...
Age (mean yr)	57.8		60.0		0.013
Men	403	(80)	13.8	(72.6)	0.038
Clinical findings					
Angina class (Canadian)					
I and II	151	(33.5)	43	(26.9)	0.123
III and IV	300	(66.5)	117	(73.1)	0.123
Angina duration (mean mo)	12.56		9.27		0.087
Rest angina	256	(52.8)	96	(53.0)	0.953
Previous MI	117	(23.2)	52	(27.4)	0.256
Diabetes	68	(13.8)	25	(13.9)	0.975
Smoking (within 1 mo)	128	(26.6)	56	(32.9)	0.115
Nitrates	384	(77.7)	149	(82.8)	0.154
Calcium antagonists	421	(85.1)	153	(84.1)	0.752
β-Blockers	241	(50.3)	78	(44.8)	0.215
Angiographic findings					
Mean pre-PTCA stenosis (%)	82.2		83.1		0.316
Mean stenosis length (mm)	5.69		5.41		0.411
Lesion location					
LCA	249	(49.5)	99	(52.7)	0.460
LCx	112	(22.3)	42	(22.3)	0.983
RCA	122	(24.3)	45	(23.9)	0.931
Graft	20	(4.0)	2	(1.1)	0.052

MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; LCA, left coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

Discussion

Several studies of induced atherosclerosis have suggested less severe atherosclerosis in cortisone-pretreated rabbits,[13–17] but other studies have not reported a beneficial effect.[23–25] This steroid has been reported to inhibit vascular smooth muscle growth and also inhibit vascular smooth muscle proliferation after balloon-induced endothelial injury.[26] Stone et al[18] randomized 52 patients to receive 125 mg methylprednisolone intramuscularly the night before and morning of repeat PTCA. These patients also took 60 mg prednisone daily for 1 week while 50 control patients received no steroids. All of these patients had restenosis following a prior PTCA. Angiographic follow-up was limited to only 53% of patients, and the restenosis rate was 36% in the steroid group and 40% in controls. Occurrence of restenosis, death, or angina class III–IV was 38% in the steroid group and 46% in controls. These differences were not statistically significant but were interpreted as suggesting a trend in favor of steroid treatment to reduce restenosis, which would require larger trials for confirmation.

Our results, from the largest, prospective, controlled trial dealing with restenosis, indicate that infusion of methylprednisolone before PTCA does not significantly influence the overall restenosis rate. No significant differences in baseline characteristics in the study groups occurred that may have obscured

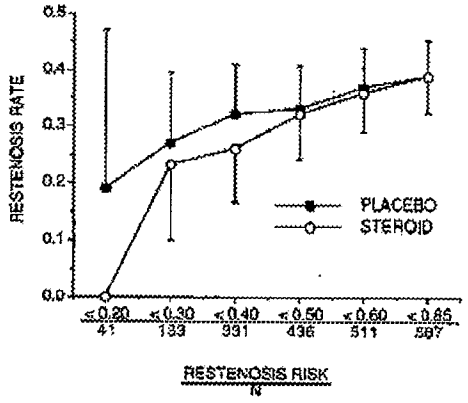

FIGURE 3. *Line plot showing effect of treatment on observed restenosis rate (y axis) according to deciles of restenosis risk (x axis) predicted by the multivariate model. A trend toward reduced restenosis rate is apparent in the steroid group (-○-) with lower-risk lesions when compared with placebo (-●-). As restenosis risk increases, however, this trend disappears. Restenosis risk was modeled as a function of percent stenosis, stenosis length, adjacent artery diameter, and post-PTCA percent stenosis. One of these variables could not be obtained in 31 total or subtotal stenoses. These lesions were not used in this analysis because restenosis risk could not be calculated. Isobars represent 95% confidence limit estimates. N, number of lesions in each decile of restenosis risk.*

corticoids,[41] but the aspirin used in our study should have inhibited platelet-derived thromboxane.

In summary, pulse methylprednisolone did not reduce the overall restenosis rate after successful PTCA, but a beneficial effect in less severe lesions could not be definitely excluded. Different mechanisms may dominate in the repair process after PTCA, depending on the degree of arterial injury caused by the balloon. In future trials designed to study restenosis, perhaps patients should be stratified, relative to restenosis risk, to permit those with differing stenosis and artery characteristics to be evaluated independently.

Appendix
M-HEART Study Group

Study Chairman

Carl J. Pepine, MD.

Clinical Sites and Investigators

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Florida Hospital, Orlando, Florida: Andrew S. Taussig, MD, Coprincipal Investigator; Hall B. Whitworth, MD, Coprincipal Investigator; William E. Story, MD, Michael Nocero, MD, and Suzanne Lee, RN.

Hospital of the University of Pennsylvania, Philadelphia: John W. Hirshfeld, Jr., MD, Principal Investigator; J. Patrick Kleaveland, MD, William G. Kussmaul, MD, Warren K. Laskey, MD, and Elliot Barnathan, MD.

Medical College of Virginia, Richmond: George Vetrovec, MD, Coprincipal Investigator; Michael J. Cowley, MD, Coprincipal Investigator; and Sharon Cole, BSN.

South Miami Hospital, Miami, Florida: James R. Margolis, MD, Principal Investigator; Jose C. Martin, MD, Dan Krauthamer, MD, and Shelley Perry, RN.

Thomas Jefferson University, Philadelphia, Pennsylvania: Sheldon Goldberg, MD, Principal Investigator; Michael P. Savage, MD, Andrew Zalewski, MD, and Pat Wilson, RN.

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Policy and Safety Board

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University of Pennsylvania, Philadelphia: Sankey Williams, MD.

Quantitative Angiographic Center

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KEY WORDS • methylprednisolone • percutaneous transluminal coronary angioplasty • steroids

Angiographic Surrogate End Points in Drug-Eluting Stent Trials: A Systematic Evaluation Based on Individual Patient Data From 11 Randomized, Controlled Trials

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CLINICAL RESEARCH — Interventional Cardiology

Angiographic Surrogate End Points in Drug-Eluting Stent Trials

A Systematic Evaluation Based on Individual Patient Data From 11 Randomized, Controlled Trials

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London, United Kingdom; New York, New York; Boston, Massachusetts; Durham, North Carolina; and Cleveland, Ohio

Objectives We sought to validate 4 angiographic measures as potential surrogates for clinical restenosis (target lesion revascularization [TLR]) after stent implantation.

Background Given the low revascularization rates with drug-eluting stents (DES), an angiographic surrogate of TLR is desirable to reduce the sample size required to demonstrate efficacy in future trials of antirestenosis devices.

Methods We evaluated 4 potential angiographic measures (late loss [LL] and percent diameter stenosis [%DS], both in-stent and in-segment) as a surrogate for TLR at 1 year. From 11 multicenter, prospective randomized stent trials, 9 comparing DES with bare-metal stents (BMS) and 2 comparing different DES, individual data on 5,381 patients with a single treated lesion and follow-up angiography at 6 to 9 months were analyzed.

Results By 4 well-defined criteria of surrogacy, LL and %DS strongly predicted the risk of TLR, with in-segment %DS being the most highly predictive (~0.95). Differences in TLR risk were fully explained statistically by their differences in LL or %DS, although LL as a surrogate was dependent on vessel size whereas %DS was not. However, because of the curvilinearity of the logistic model, trials comparing 2 effective DES can have significant differences in mean LL and %DS but small expected differences in TLR risk, especially at the lower ranges of LL and %DS.

Conclusions From in-stent and in-segment LL and %DS measures, logistic models can reliably estimate TLR rates for DES and BMS. These angiographic measures are thus suitable surrogate markers for clinical stent efficacy and can be used as primary end points in future DES trials to significantly reduce sample size. (J Am Coll Cardiol 2008; 51:23–32) © 2008 by the American College of Cardiology Foundation

Drug-eluting stents (DES) reduce angiographic restenosis in patients undergoing percutaneous coronary intervention (PCI). The most commonly measured clinical indicator of stent efficacy is target lesion revascularization (TLR), which is defined as recurrent ischemia due to angiographic restenosis within the stent or its margins necessitating repeat revascularization with either PCI or coronary artery bypass graft surgery. Of note, TLR rates are typically 30% to 60% lower than the corresponding binary restenosis rates, suggesting discordance between the ischemic thresholds of angiographic and clinical measures of restenosis (1,2).

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Given the low rates of TLR after bare-metal stent (BMS) implantation in the relatively noncomplex lesions typically studied in stent trials, more than 2,000 enrolled patients are required in randomized trials to demonstrate a clinically

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
%DS = percent diameter stenosis
LL = late loss
MLD = minimal lumen diameter
PCI = percutaneous coronary intervention
RVD = reference vessel diameter
TLR = target lesion revascularization

relevant 30% reduction in TLR with DES. Moreover, given the low frequency clinical event rates with DES, very large potential differences between stents (the "delta") often are allowed in noninferiority trials to make comparative DES studies practical, degrading confidence that the clinical performance of 2 devices are indeed similar.

To reduce the sample size required in superiority and noninferiority trials, continuous angiographic indexes of long-term stent patency such as late lumen loss (LL) and follow-up percent diameter stenosis (%DS) have been proposed as surrogates of TLR for use in randomized studies (3–5). However, previous DES studies have suggested that the distribution of individual LL measures is asymmetric with a rightward skew and that the relation between LL and TLR is nonlinear (6,7). Whether angiographic measures are thus valid surrogates for TLR and, if so, what cutoff values correspond with clinical efficacy has not been established. These issues have important clinical and regulatory implications.

To address these issues, we systematically analyzed pooled patient-level data from 11 randomized, controlled DES trials. Specifically, we sought to determine the appropriateness of using the continuous angiographic end points of LL and follow-up %DS as surrogates of TLR after stent implantation; to characterize the relationship between clinical and angiographic measures of stent efficacy; and to assess the relative value in this regard of in-stent versus in-segment measures.

Methods

Study population and protocols. Eleven randomized stent trials enrolling 8,726 patients were included in the analysis Details of the study protocols have been reported previously (8–18). Protocol-specified angiographic follow-up was performed in a cohort of patients of varying size from each of these studies to further characterize vascular responses. In total, routine angiographic follow-up between 6 and 9 months and clinical follow-up at 1 year was performed in 5,381 patients with a single treated lesion, who comprise the study population (Table 1). All patients at baseline had symptoms or objective signs of myocardial ischemia due to coronary artery disease and at least one de novo stenosis in a native coronary artery treated with 1 or more study stents. Nine of the 11 randomized trials compared DES versus otherwise-identical BMS (8–16), and the remaining 2 trials compared 1 DES to another DES (Cypher vs. Taxus in REALITY; Prospective Randomized Multi-Center Head-to-Head Comparison of the Sirolimus-Eluting Stent [Cypher] and the Paclitaxel-Eluting Stent [Taxus] and Endeavor vs. Cypher in ENDEAVOR III; Randomized Comparison of Zotarolimus-Eluting and Sirolimus-Eluting Stents in Patients With Coronary Artery Disease) (17,18). In total, the pooled analysis comprised 6 arms treated with sirolimus-eluting stents (Cypher, Cordis Corp., Miami, Florida) (8–10,13,17,18), 5 arms using paclitaxel-eluting stents (4 with the polymer-based Taxus stent [Boston Scientific, Natick, Massachusetts]) (11,14,15,17), and 1 with a nonpolymeric paclitaxel-eluting stent (Achieve, Guidant, Indianapolis, Indiana) (12); 2 arms using zotarolimus-eluting stents (Endeavor, Medtronic, Minneapolis, Minnesota) (16,18), and 9 arms using bare metal stents (BX Velocity, Cordis Corp.; Express, Boston Scientific; Multilink Penta, Guidant, Indianapolis, Indiana; Driver, Medtronic) (8–16).

Table 1 Characteristics of Studies Included in Pooled Analysis

Trial Name	Arm 1	Arm 2	Study Design	No. of Patients†	Recruiting Centers	Diabetes Mellitus, %	Reference Vessel Diameter, mm	Lesion Length, mm
TAXUS-IV	Taxus (SR)	Express*	R, DB, MC	558	U.S.	24.4	2.78 ± 0.48	13.8 ± 6.6
TAXUS-V	Taxus (SR)	Express*	R, DB, MC	989	U.S.	31.3	2.69 ± 0.57	17.2 ± 9.2
TAXUS-VI	Taxus (MR)	Express*	R, DB, MC	417	Europe	18.9	2.80 ± 0.47	20.6 ± 7.5
SIRIUS	Cypher	BX Velocity*	R, DB, MC	699	U.S.	26.6	2.81 ± 0.46	14.6 ± 5.9
E-SIRIUS	Cypher	BX Velocity*	R, DB, MC	319	Europe	23.3	2.55 ± 0.36	15.2 ± 6.2
C-SIRIUS	Cypher	BX Velocity*	R, DB, MC	88	Canada	26.1	2.64 ± 0.33	13.2 ± 5.7
RAVEL	Cypher	BX Velocity*	R, DB, MC	218	Europe	18.9	2.65 ± 0.45	9.7 ± 3.3
DELIVER	Achieve	ML Penta*	R, SB, MC	442	U.S.	N/A	2.96 ± 0.51	11.5 ± 4.6
REALITY	Cypher	Taxus, (SR)	R, UB, MC	756	Europe + LA + Asia	24.9	2.42 ± 0.47	18.4 ± 9.4
ENDEAVOR II	Endeavor	Driver*	R, DB, MC	521	Europe + AP + Aus + Canada	20.2	2.76 ± 0.47	13.8 ± 5.3
ENDEAVOR III	Endeavor	Cypher	R, SB, MC	374	U.S.	28.6	2.78 ± 0.46	15.1 ± 6.7

*Bare-metal stent. All other stents are drug-eluting stents. †Only patients with a single lesion treated and follow-up angiography are included in this analysis.

AP = Asia Pacific; Aus = Australia; DB = double-blind; DM = diabetes mellitus; ENDEAVOR = Randomized Comparison of Zotarolimus-Eluting and Sirolimus-Eluting Stents in Patients With Coronary Artery Disease; LA = Latin America; MC = multicenter; MR = moderate release; R = randomized; RAVEL = A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization; REALITY = Prospective Randomized Multi-Center Head-to-Head Comparison of the Sirolimus-Eluting Stent (Cypher) and the Paclitaxel-Eluting Stent (Taxus); SB = single-blind; SIRIUS = Sirolimus-Eluting Stent in Coronary Lesions; SR = slow release; TAXUS = Paclitaxel-Eluting Stents in the Treatment of Longer Lesions. Focus on Patients With Diabetes; UB = unblended.

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A wide range of de novo lesions in native coronary arteries were evaluated in these trials. Earlier pivotal studies enrolled patients with relatively simple lesions (RAVEL [A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization], SIRIUS [Sirolimus-Eluting Stent in Coronary Lesions], TAXUS-IV [Paclitaxel-Eluting Stents in the Treatment of Longer Lesions. Focus on Patients With Diabetes], DELIVER, ENDEAVOR II and III) (8,9,11,12,16,18). Later studies enrolled patients with more complex lesions potentially having greater risk of restenosis, including E-SIRIUS, C-SIRIUS, TAXUS-V, and REALITY, which targeted lesions in small vessel (<3.0 mm in diameter) (10,13,14,17), and TAXUS-V, TAXUS-VI, and REALITY, which enrolled patients with long lesions (>30 mm in length) (14,15,17). Inclusion of bifurcations and ostial lesions was also allowed in the REALITY trial (17). All other studies excluded complex stenoses such as ostial, bifurcation, excessive calcification, total occlusions, and thrombus-containing lesions. In TAXUS-V, TAXUS-VI, all the SIRIUS trials, and REALITY trial, the use of multiple stents was allowed (9,10,13–15,17). In most studies, conventional stent implantation with predilation was mandated (8,9,11,12,14–16,18). Direct stenting was allowed only in E-SIRIUS, C-SIRIUS, and REALITY (10,13,17). Only the REALITY trial allowed the enrolment of patients with multiple lesions (17). From the REALITY database, only patients undergoing stent implantation in a single lesion were included in the present analysis.

Target lesion revascularization was defined as the need for repeat revascularization at the site of stent implantation, including the 5 mm proximal and distal peristent zones, with either associated ischemia or a severe follow-up %DS (>70% by quantitative angiography). Independent clinical event committees for each trial adjudicated all TLR events.

Angiographic analysis methodology. All angiograms were analyzed by independent core laboratories: the Brigham and Women's Hospital, Boston, Massachusetts (9–11,13–16,18), Cardiovascular Research Foundation, New York, New York (12), and Cardialysis, Rotterdam, the Netherlands (8,17). Similar methodology was used in all 3 laboratories. Quantitative coronary angiography was performed with the CMS Medis system (Leiden, the Netherlands) in all studies but 2, in which the CASS system (PIE Medical, Maastricht, the Netherlands) was used (8,17). Measurements of minimal lumen diameter (MLD) and reference vessel diameter (RVD) were performed at baseline, after final intervention and at follow-up, and used to calculate the %DS = (1 − MLD/RVD) × 100. In 9 trials, the RVD was obtained from averaging 5-mm segments proximal and distal to the target lesion location, whereas the interpolated RVD at the lesion site was used to calculate %DS in 2 trials (8,17). We calculated LL as the change in MLD from the final post-PCI angiogram to follow-up, and it was calculated both in-stent and in the entire analysis segment, also including the 5-mm proximal and distal stent margins (also called in-segment).

Statistical methods. All statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, North Carolina). The statistical criteria for evaluating whether LL and follow-up %DS are useful surrogate end points for TLR entailed 4 main steps, as follows.

DETERMINATION OF WHETHER THE POTENTIAL SURROGATE EXHIBITS STRONG CONSISTENT EVIDENCE OF TREATMENT DIFFERENCES WITHIN EACH TRIAL. For this purpose, the z-score was used, defined as the observed treatment difference divided by its standard error. For LL and %DS, this was the t statistic obtained from a 2-sample t test modified to permit unequal variances in the 2 treatment groups. For comparative purposes, the z-score also was obtained for the treatment difference in percentage with TLR. For such a difference in percentages, z is the square-root of the chi-square statistic. The larger the value of z, the stronger the evidence of a treatment difference (e.g., z scores of 1.96, 3.29, and 6.11 are associated with p values of 0.05, 0.001, and 0.000000001, respectively).

EXAMINATION OF THE STRENGTH OF THE RELATIONSHIP BETWEEN THE POTENTIAL SURROGATE (LL OR %DS) AND THE CLINICAL OUTCOME (TLR). For the patients in each clinical trial, the c-statistic was used to measure the strength of association between each quantitative outcome (e.g., in-stent LL) and the binary outcome TLR. The c-statistic is defined as the area under the receiver operator characteristic curve but can be more clearly understood as follows: for any 2 randomly selected patients, one with and one without TLR, c is the probability that the former has the greater value of the quantitative surrogate. A value of c = 1 means perfect discrimination, so an effective surrogate has a value of c close to 1.

The relationship of TLR to each of the 4 potential surrogates LL and %DS, both in-stent and in-segment is modeled using logistic regression applied to all 5,381 patients in the 11 trials. For a given LL the log odds of TLR depends on the RVD, and this necessitates a bivariate logistic regression in which the log odds of TLR are linearly related to LL and to RVD grouped in 3 intervals, <2.5 mm, 2.5 to 3 mm, and ≥3 mm. These logistic models (1 for each of the 4 potential surrogates) are then used to predict each individual patient's probability of TLR. For each treatment group in each trial, the predicted number with TLR equals the sum of these individual probabilities. Actual and predicted percentages of patients with TLR for all 22 treatment groups in the 11 trials are then compared to examine the extent to which the potential surrogate can reliably predict the TLR rate in these trials, and hence can be relied on to predict the true expected TLR rate in any future trials in which TLR might not be actually assessed.

Table 2 LL, Follow-Up %DS, and 1 Year TLR Rates

	LL, mm				%DS					
	In-Stent		In-Segment		In-Stent		In-Segment		TLR Rate, %	
Trial Name	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2
TAXUS-IV	0.39 ± 0.50	0.92 ± 0.58	0.23 ± 0.44	0.61 ± 0.57	17.4 ± 17.7	37.2 ± 19.8	26.3 ± 15.4	37.8 ± 18.5	5.3	16.5
TAXUS-V	0.49 ± 0.61	0.90 ± 0.62	0.33 ± 0.54	0.60 ± 0.59	23.1 ± 24.6	38.9 ± 24.8	33.6 ± 21.8	42.3 ± 22.3	11.2	19.0
TAXUS-VI	0.39 ± 0.56	0.99 ± 0.59	0.24 ± 0.57	0.66 ± 0.62	22.2 ± 19.2	42.8 ± 20.9	30.4 ± 17.4	45.4 ± 19.7	8.7	20.3
SIRIUS	0.17 ± 0.45	1.00 ± 0.70	0.24 ± 0.47	0.81 ± 0.67	10.4 ± 16.5	40.3 ± 25.3	23.6 ± 16.4	43.4 ± 22.5	4.9	20.2
E-SIRIUS	0.21 ± 0.41	1.06 ± 0.61	0.19 ± 0.41	0.82 ± 0.58	14.6 ± 16.0	47.5 ± 24.7	24.6 ± 14.6	48.8 ± 23.3	4.6	24.9
C-SIRIUS	0.08 ± 0.33	1.02 ± 0.69	0.09 ± 0.31	0.79 ± 0.74	9.3 ± 10.6	44.2 ± 26.5	20.5 ± 10.3	47.8 ± 24.5	4.0%	22.0%
RAVEL	−0.01 ± 0.33	0.80 ± 0.53	−0.05 ± 0.30	0.47 ± 0.47	14.7 ± 7.0	36.7 ± 18.1	25.3 ± 9.6	38.7 ± 16.9	0.8%	13.7%
DELIVER	0.81 ± 0.60	0.98 ± 0.57	0.43 ± 0.57	0.56 ± 0.59	30.9 ± 20.8	36.2 ± 20.9	34.7 ± 19.1	38.9 ± 20.1	8.8%	12.1%
REALITY	0.09 ± 0.38	0.30 ± 0.42	0.04 ± 0.35	0.16 ± 0.39	26.5 ± 14.9	22.8 ± 15.1	28.2 ± 14.5	30.9 ± 14.9	4.4%	5.3%
ENDEAVOR II	0.61 ± 0.46	1.03 ± 0.59	0.35 ± 0.47	0.72 ± 0.61	27.7 ± 17.5	42.4 ± 21.7	32.6 ± 16.4	44.5 ± 20.4	6.0%	13.2%
ENDEAVOR III	0.60 ± 0.48	0.15 ± 0.35	0.34 ± 0.44	0.12 ± 0.33	24.3 ± 17.1	11.2 ± 16.0	29.9 ± 15.3	23.8 ± 14.0	6.9%	3.6%

Values are expressed as % where indicated or as mean ± SD.
%DS = percent diameter stenosis; LL = late loss; TLR = target lesion revascularization; other abbreviations as in Table 1.

DETERMINATION OF WHETHER THE POTENTIAL SURROGATE IN EACH CLINICAL TRIAL STATISTICALLY EXPLAINS THE OBSERVED TREATMENT DIFFERENCE IN THE CLINICAL OUTCOME. The Prentice criterion of surrogacy (19) entails fitting 2 logistic regression models to all the data within a trial comparing DES and BMS: 1) log odds TLR = $\alpha 1 - \beta 1$ T, where T = 1 if DES, 0 if BMS; and 2) log odds TLR = $\alpha 2 - \beta 2$ T − $\gamma \times$ potential surrogate (e.g., in stent LL). Then, the estimated percentage of treatment effect explained by the surrogate = $100 \times (\beta 1 - \beta 2)/\beta 1$ %. With a perfect surrogate, the true amount explained should be 100%. The Prentice criterion of surrogacy was explored in the 5 largest trials comparing DES and BMS, as this criterion is best explored in large trials in which treatment differences in the clinical outcome TLR are very pronounced.

DETERMINATION OF WHETHER THE EXTENT OF THE SIZE OF THE TREATMENT EFFECT ON TLR LINKS CLOSELY TO THE SIZE OF THE TREATMENT EFFECT ON THE POTENTIAL SURROGATE (E.G., IN-SEGMENT LL) ACROSS ALL THE TRIAL STUDIES. The Hughes criterion (20) of surrogacy was used to demonstrate across trials the extent to which the magnitude of treatment effect on TLR is closely linked to the magnitude of mean treatment difference in the quantitative potential surrogates LL and %DS. This is best examined graphically by plotting on a single scatter graph the %TLR on the vertical axis and the mean of the potential surrogate on the horizontal axis for each treatment group in each of the 11 trials.

Results

The included studies and characteristics of patients with a single treated lesion and angiographic follow-up are shown in Table 1. Table 2 provides the LL, follow-up %DS, and 1-year TLR rates for each of the 11 trials.

Treatment difference in %DS, LL, and TLR in each trial. For each of the 11 trials, the strength of evidence for a treatment difference in LL and %DS (both in-stent and -segment) expressed by the z-score (the observed difference in means divided by its standard error) is summarized in Table 3. As shown in this table, the z-scores for LL and follow-up %DS are similar (and markedly greater than the z-scores for TLR), signifying that LL and %DS discriminate equally well between treatment groups and much more significantly so than does TLR. For both LL and %DS, the z-scores were greater for the in-stent compared with the in-segment measure.

The relationship of LL and follow-up %DS to the clinical outcome TLR. The c-statistic expresses the strength of association of TLR to each of the 4 potential surrogate end points (Table 4) and was examined for each trial separately with individual patient data in both treatment

Table 3 *Z*-Scores* for Treatment Difference in LL and Follow-Up %DS), Each for In-Stent and In-Segment, and TLR for 11 Randomized Trials of Drug-Eluting Stents

	In-Stent		In-Segment		
Trial	LL	%DS	LL	%DS	TLR
TAXUS-IV	11.6	12.5	8.9	9.4	4.7
TAXUS-V	10.5	10.0	7.3	6.2	4.0
TAXUS-VI	10.6	10.5	7.2	8.2	3.6
SIRIUS	18.7	18.5	13.1	13.3	7.1
E-SIRIUS	14.5	14.0	11.1	11.0	6.1
C-SIRIUS	8.2	8.1	5.8	6.8	3.1
RAVEL	13.7	11.9	9.8	7.2	3.8
DELIVER	3.0	2.7	2.3	2.3	1.3
REALITY	7.4	3.3	4.5	2.5	1.1
ENDEAVOR II	9.2	8.5	7.7	7.3	4.0
ENDEAVOR III	8.3	6.5	4.4	3.4	1.1

*z = difference in treatment means (or percentages) divided by its standard error and summarizes the strength of evidence for a treatment difference. z = 1.96, 3.29, and 6.11 correspond to p = 0.05, 0.001, and 0.000000001, respectively.
Abbreviations as in Tables 1 and 2.

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Table 4 c-Statistics Summarizing the Strength of Association of TLR With Each of the 4 Potential Surrogate End Points With Data for All Patients (Both Groups Combined) in Each Trial

	In-Stent		In-Segment	
Trial	LL	%DS	LL	%DS
TAXUS-IV	0.90	0.94	0.92	0.97
TAXUS-V	0.88	0.90	0.91	0.95
TAXUS-VI	0.86	0.87	0.89	0.95
SIRIUS	0.88	0.90	0.92	0.95
E-SIRIUS	0.94	0.95	0.92	0.95
C-SIRIUS	0.86	0.86	0.93	0.94
RAVEL	0.98	0.93	0.91	0.95
DELIVER	0.85	0.86	0.86	0.91
REALITY	0.90	0.93	0.93	0.98
ENDEAVOR II	0.88	0.91	0.88	0.95
ENDEAVOR III	0.77	0.80	0.93	0.95
Averaged	0.88	0.90	0.91	0.95

Abbreviations as in Tables 1 and 2.

groups combined. The highest c-statistic in most trials was for the association of the in-segment %DS to TLR, with average c = 0.95 across all 11 trials. The c-statistics relating TLR to the other 3 measures (in-stent LL, in-stent %DS, and in-segment LL) were slightly smaller, but similar to one another, with average c ≈ 0.90 across all 11 trials.

Figure 1, which combines data from all 11 trials, shows the observed proportions with TLR for 12 intervals of LL and 10 intervals of follow-up %DS. For the latter, it is evident that for any given LL the risk of TLR depends on the RVD, whereas the relationship between follow-up %DS and TLR does not depend on vessel size. A sharp monotonic increase in the risk of TLR was present once follow-up %DS reaches 50% up to a TLR rate of 90% for patients with %DS between 70% and 90%. For the small number of patients with %DS ≥90%, the observed TLR rate decreased to 63%.

Logistic regression was used to model the relation between the 4 angiographic surrogates and TLR, adjusting for vessel size (RVD). The consequent smooth logistic curves are shown in Figure 1. The actual regression equations relating in-stent LL and in-segment %DS to TLR are given in the Online Appendix.

Table 5 shows the predicted number of patients with TLR (based on the aforementioned logistic model of in-stent LL and in-segment %DS) for each treatment group in the 11 trials compared with the actual observed numbers. Close agreement between predicted and actual numbers was present in all 44 instances, indicating that the models have excellent goodness of fit. This is further illustrated in the upper graph of Figure 2, which plots the actual TLR versus in-stent LL predicted TLR rates for all 22 treatment groups (13 DES and 9 BMS). All points are within one standard error of the 45° diagonal line of equality. Similar results were obtained when the predicted percent with TLR was based on a logistic model relating risk of TLR to in-segment follow-up %DS (Fig. 2, lower graph).

Relationship between treatment differences in TLR and LL or %DS. Applying the Prentice criterion of surrogacy to the 5 largest trials comparing DES and BMS, we present in Table 6 for each trial the percentage of treatment effect on TLR that is explained by each of the four potential surrogate outcomes. In-segment LL and follow-up %DS each explain most of the treatment effect in TLR, such that in each trial any residual treatment effects on TLR, after accounting for the influence of LL and %DS, fall well short of statistical significance. In-stent LL and follow-up %DS were both estimated to explain all of the treatment effect in most of the trials. This unusual phenomenon may be because in-stent measures reflect "pure efficacy" without taking account of edge effects, and hence tend to slightly exaggerate the overall superiority of DES compared with BMS.

Relating the size of treatment effect on TLR to the size of treatment effects on LL and %DS. Applying the Hughes criterion of surrogacy, in Figure 3 we show the reductions in mean LL and mean follow-up %DS (both in-stent and in-segment) that were achieved for each trial of a DES compared with a BMS were clearly related to a corresponding reduction in risk of TLR. Of the 4 plotted associations in Figure 3, the tightest link to TLR reduction is seen for in-segment LL. In contrast, in the REALITY trial, which compared 2 DES with relatively low LL, the rates of TLR were similar with the 2 devices despite a highly significant difference in in-stent and in-segment mean LL and follow-up %DS.

Discussion

Before the availability of DES, the major limitation of PCI was restenosis, which necessitated repeat intervention in 20% to 30% of cases after BMS implantation (21). In contrast, currently approved DES are notable for much lower rates of clinical and angiographic restenosis in the mostly noncomplex lesion types enrolled in the pivotal randomized trials and, as a result, DES have been widely adopted for the majority of patients undergoing PCI. This new standard of care has made it difficult to realistically evaluate next-generation DES and novel antirestenosis therapies because the frequencies of the customary measures of clinical effectiveness (such as TLR) are so low that very large sample sizes are required for superiority and noninferiority testing. Although this problem may be overcome by restricting enrolment to high-risk lesions and patients, recruitment rates would markedly slow, and the results would not be applicable to a broader cross section of patients. Thus, the need exists for alternative measures that can reliably be used as surrogates for TLR, allowing smaller trial sizes to accelerate evaluation of potentially more efficacious and cost-effective DES alternatives.

Ellis et al. (6) previously demonstrated a strong association between the continuous angiographic measure of

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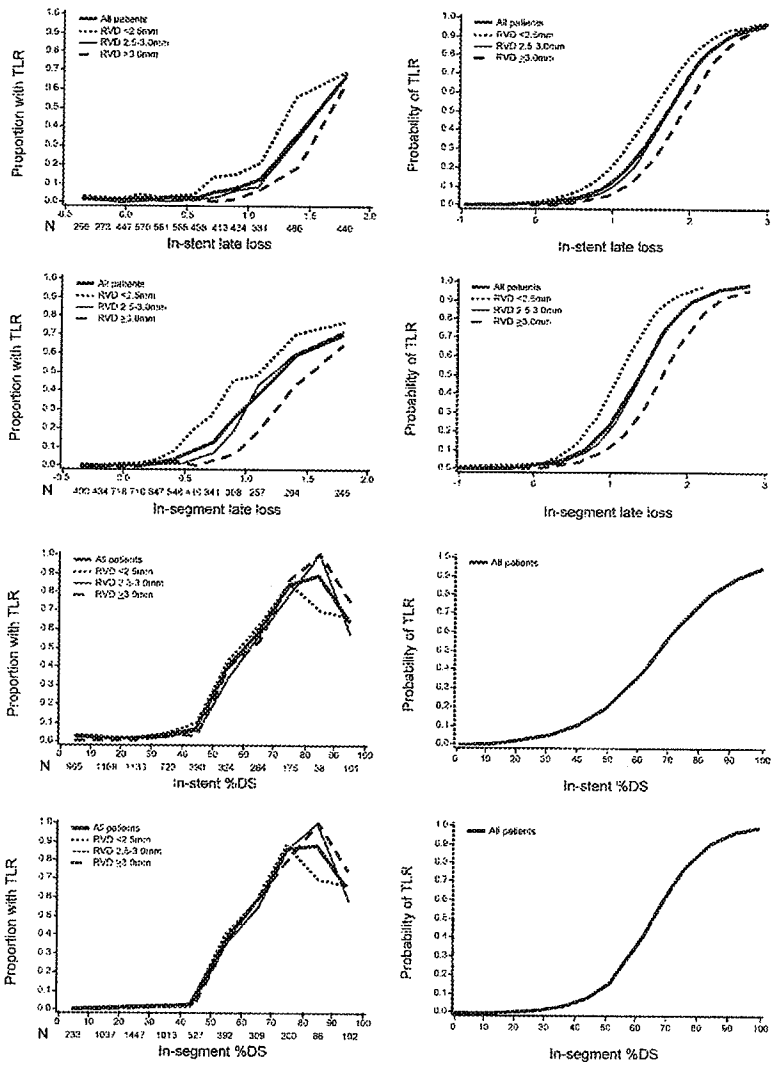

Figure 1 **Impact of Angiographic Measures on TLR**

Proportion of patients with target lesion revascularization (TLR) as a function of in-stent and in-segment late loss (LL) and follow-up percent diameter stenosis (%DS), stratified by reference vessel diameter (RVD) using individual patient data from all 11 trials. **Left column** = observed proportions with TLR for 12 intervals of LL and 10 intervals of follow-up %DS. **Right column** = corresponding smoothed logistic curves.

LL and individual risk of TLR. However, this analysis was limited by modest sample size from a single study (TAXUS-IV). The present report describing the detailed results of a pooled patient level analysis from 11 randomized contemporary DES trials involving 5,381 patients with systematic angiographic follow-up is the most extensive investigation to date evaluating the potential utility of angiographic surrogates of TLR. This analysis demonstrates that by 4 different commonly accepted criteria of surrogacy, both LL and follow-up %DS, whether measured in-stent or in-segment, are valid surrogates for TLR. The risk of TLR in individual patients is strongly related to LL and %DS. Also, the treatment differences in TLR rates within each trial were entirely explained by treatment differences in LL and %DS. This strong of a linkage has rarely been observed in other fields; for example, blood pressure differences between antihypertensive regimens do not fully explain their differences in risk of stroke (22). Finally, the size of the treatment differences in %TLR linked closely to the respective size of the mean differences for these surrogate markers, especially for in-segment LL (20).

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Table 5 Comparison of Actual and LL-Predicted Numbers of Patients With TLR in 22 Treatment Groups in 9 Trials, Based on Logistic Model Corrected for Vessel Size

Trial	Drug-Eluting Stents			Bare-Metal Stents		
	Actual	Predicted From In-Stent LL	Predicted From In-Segment %DS	Actual	Predicted From In-Stent LL	Predicted From In-Segment %DS
TAXUS-IV	16	17.8	15.5	48	47.4	40.1
TAXUS-V	51	50.4	61.6	96	96.2	100.3
TAXUS-VI	18	13.6	17.7	45	42.8	44.3
SIRIUS	20	11.6	17.0	86	79.0	75.6
E-SIRIUS	6	6.2	6.4	44	43.9	44.6
C-SIRIUS	1	0.8	0.7	10	11.7	13.0
RAVEL	1	1.6	2.2	16	15.0	13.2
DELIVER	29	30.8	26.5	37	38.6	32.6
ENDEAVOR II	18	24.0	21.6	49	58	56.5
REALITY, Cypher arm	12	11.0	20.3	—	—	—
REALITY, Taxus arm	21	19.1	23.7	—	—	—
ENDEAVOR III, Endeavor arm	20	25.9	18.2	—	—	—
ENDEAVOR III, Cypher arm	4	2.7	3.2	—	—	—

Abbreviations as in Tables 1 and 2.

LL as a surrogate of clinical stent efficacy. The relationship between individual patient LL and risk of TLR was found to be well represented by a logistic curve, confirming the observation introduced by Ellis and co-workers (6). Although LL would thus appear to be a useful surrogate marker for TLR in DES versus BMS trials, the nonlinearity of this relationship makes the use of LL as a surrogate in comparative DES versus DES studies more problematic. In REALITY, despite the highly significant difference in both in-stent and in-segment late loss between Cypher and Taxus, the 1-year rates of TLR were similar: 4.4% versus 5.3%, respectively. Conversely, the large difference in LL between the Cypher and Endeavor stents in the ENDEAVOR III trial was associated with a larger relative difference in TLR between the two stents (3.6% with Cypher and 6.9% with Endeavor). This disparity between REALITY and ENDEAVOR III may be explained by the fact that the greater LL of the Endeavor stent places it on the rising slope of the LL-TLR relation, whereas the mean LL of Cypher and Taxus place the majority of patients on the flatter part of the curve where similar absolute differences in LL translate into smaller differences in TLR.

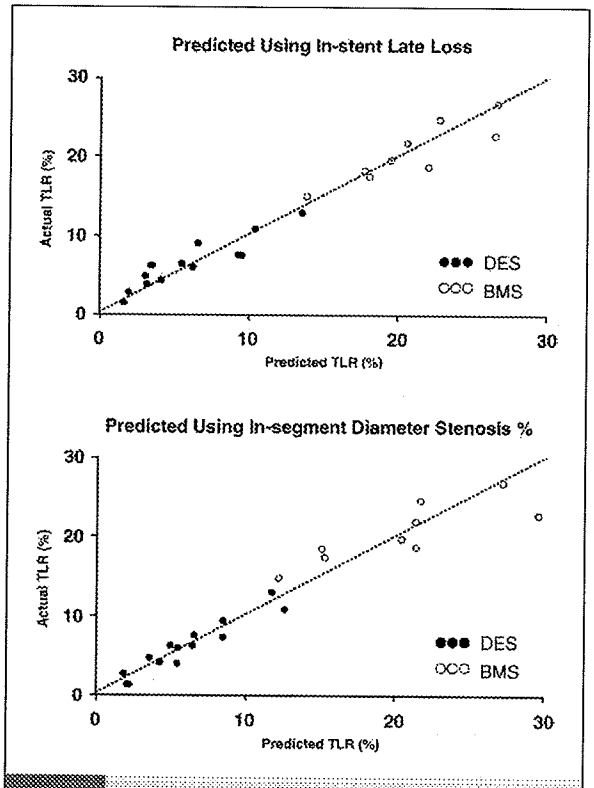

Figure 2 Actual Versus Predicted Rates of TLR

Actual versus predicted rates of TLR for 22 treatment groups (13 with drug-eluting stents [DES], 9 with bare-metal stents [BMS]), using logistic models for in-stent LL **(top)** and follow-up %DS **(bottom)**. Abbreviations as in Figure 1.

Table 6 The Percentage of Treatment Effect on TLR Explained by Each of 4 Potential Surrogate Outcomes* in the 5 Largest Trials Comparing Drug-Eluting and Bare-Metal Stents: Percent Treatment Effect Explained

Trial	In-Stent		In-Segment	
	LL	%DS	LL	%DS
TAXUS-IV	98	138	83	83
TAXUS-V	101	94	82	47
TAXUS-VI	115	124	75	114
SIRIUS	132	142	91	103
ENDEAVOR II	100	119	82	107

*100% explained means that in a logistic model for log odds of TLR the coefficient for treatment effect becomes 0 when the potential surrogate (e.g., LL) is added as a second predictor variable. More than 100% explained means that the coefficient for treatment effect has changed sign.
Abbreviations as in Tables 1 and 2.

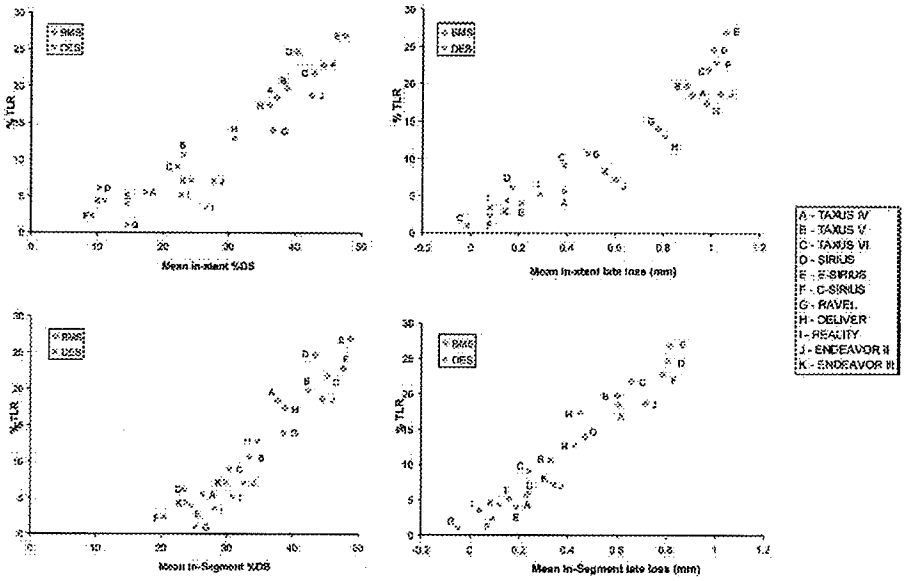

Figure 3 Relationship Between Angiographic Measures and Actual TLR

Relationship of TLR to mean LL and mean follow-up %DS both in-stent and in the analysis segment for each stent treatment group in 11 randomized trials. Abbreviations as in Figures 1 and 2.

Follow-up %DS as a surrogate of clinical stent efficacy. Follow-up %DS was equally effective as LL in predicting TLR. The risk of TLR was small and nearly flat at less than 50% DS, increased sharply between %DS of 50% to 80%, and then reached a plateau at greater than 80% DS. Of note, the TLR rate decreased to approximately 63% for the small number of occluded (or near-occluded) vessels, which likely is explained by physician decision to treat approximately one-third of such patients conservatively if clinically stable or with a low likelihood of sustained vessel patency with repeat revascularization.

The present study demonstrates that %DS and LL are roughly equally effective surrogates. However, although it has been argued that LL best captures the physiological mechanism whereby stents reduce TLR (3–5), several advantages favor the use of %DS in practice. First, and perhaps most importantly, the impact of LL on the likelihood of TLR varies with vessel size, whereas the %DS–TLR relationship is vessel size independent. Second, as the difference in 2 measures of MLD obtained from 2 different angiograms at different points in time, LL is inherently subject to more measurement error than follow-up %DS. In contrast, %DS is based on evaluation at a single time point. Finally, %DS is conceptually more intuitive and easier to apply in clinical practice than LL.

In-stent versus in-segment measures as angiographic surrogates. In-stent LL and follow-up %DS measurements both assess the magnitude of absolute and relative neointimal hyperplasia within the stent, providing an accurate assessment of the antiproliferative effect of DES. However, in-stent measures reflect only the pure biologic potency of an antirestenotic device. In-segment measurements additionally account for the magnitude of lumen renarrowing that occurs at the margins of the stent, which may reflect stent/balloon mismatch, drug diffusion effects, and so on. Because isolated stenoses at stent edges represent an increasingly greater proportion of TLR events with DES than BMS (9,11), in-segment measures might be a wise choice as a clinical event surrogate.

Use of quantitative angiographic measures to reduce clinical trial sample size requirements. Both %DS and LL had significantly greater ability to discriminate between treatments as compared with relying on the binary outcome TLR. For instance, in each of the 5 largest trials comparing DES and BMS, the z-score for TLR was slightly more than half of the z-score for in-segment LL, with a mean ratio of 0.54. As a result, markedly fewer patients would be required in a clinical trial to demonstrate efficacy using any of the quantitative angiographic measures as primary end point rather than binary TLR. Specifically, the number of patients required to detect a statistically significant treatment difference is inversely proportional to the square of the expected z-score. Hence, future trials comparing stents would require approximately 71% fewer patients using in-segment LL rather than TLR as the efficacy measure ($1 - 0.54^2 \times 100 = 71\%$). As discussed previously, however, for comparisons of 2 DES, both with relatively low LL, the detection of

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significant differences in LL or follow-up %DS does not imply that sizeable differences in TLR exist.

It should be noted that the logistic models in the present report describe the relationship between individual angiographic measures (LL and %DS) and the clinical efficacy variable TLR. The logistic models cannot be used to predict the expected TLR rate of a specific stent cohort by simply using the observed group mean LL or %DS, which ignores the width and skewness of the distribution. The predictive logistic models in Figure 1 and the Online Appendix may be directly applied, however, to any individual patient's angiographic data to provide an estimated probability of TLR. To determine the predicted %TLR for an entire study group, the probability of TLR for each patient is then averaged across the entire study cohort to determine the expected group TLR rate. Such an approach is a more direct use of the observed trial data rather than relying on the mean LL or %DS, and avoids the need for more complex power transformations to remove skewness (3–5).

Limitations of angiographic surrogates of TLR. Follow-up angiography in large studies is always <100% complete, most commonly because asymptomatic patients refuse restudy. However, angiographic follow-up rates in the prespecified angiographic cohorts were >80% in most of the studies in the present pooled analysis. We would thus recommend that future trials using angiographic measurements as surrogates require similarly high rates of angiographic follow-up to achieve reliable conclusions. A potential second limitation is that 3,345 of the 8,726 patients were not enrolled in the angiographic follow-up cohort of the randomized trials. However, because consecutive patients from each trial were enrolled in each angiographic substudy, it is likely that the study cohort of the present analysis is representative. Third, although blinded clinical event committees adjudicated all cases of TLR with discretion to include only events with documented ischemia, some TLR events were driven by angiographic follow-up alone in asymptomatic patients with a severe %DS (>70% by core lab assessment, which typically corresponds to a >85% operator assessed visual stenosis), with the rationale that these patients would soon likely become symptomatic and require revascularization. The exact frequency of which this "oculostenotic reflex" contributed to reported TLR rates in all the studies is unknown, but was ~10% in the TAXUS-II, -IV, -V, and -VI trials (G. Stone, unpublished data, March 1, 2007) and is thus unlikely to have materially impacted the present analysis. Nonetheless, the angiographic measures discussed herein may be considered surrogates for either ischemia-driven TLR, or in a small proportion of patients, a severe recurrent angiographic stenosis (the prevention of which is also desirable). Moreover, routine angiographic follow-up increases TLR event rates in patients receiving both BMS and DES, though to a similar relative degree (1). These biases may somewhat accentuate the magnitude of the TLR relationship with LL and %DS. TLR itself is also an imperfect measure of recurrent ischemia since the decision whether or not to perform revascularization can be affected by patient and physician preferences. In addition, LL and %DS are surrogates only of TLR after stent implantation and not of the need for future revascularization elsewhere in the coronary tree from pre-existing or progressive atherosclerosis in nonstented segments.

Finally, an important caveat when considering the use of angiographic efficacy surrogates to reduce clinical sample size in new device trials is that the ability to detect differences in relatively low frequency safety events between 2 antirestenosis therapies (for which there are no acceptable angiographic surrogate measures) will be diminished. For example, previous large randomized trials demonstrated that the achievement of greater luminal dimensions with directional atherectomy compared with balloon angioplasty was associated with an increase in periprocedural myocardial infarction (23); such a relationship might have been missed in a smaller trial powered for angiographic end points only. Additional strategies are thus needed to ensure new device safety, such as large-scale, simple randomized trials without planned follow-up angiography, or observational patient registries. In this regard, emerging devices could first be evaluated in modest-sized phase 2 studies with routine angiographic follow-up to demonstrate antirestenotic efficacy as a surrogate of low clinical TLR. Once a device has passed this first "screening" test, a larger-scale pivotal study (without follow-up angiography) could then be performed with primary safety end points. Conversely, if the angiographic surrogate end points for clinical efficacy are not met in the initial study, resources can then be diverted toward the development of more beneficial devices to improve patient outcomes.

Conclusions

Applying well-defined rigorous criteria to an extensive database of randomized trials, we have demonstrated that within certain constraints, LL and follow-up %DS are suitable surrogate markers for TLR in trials evaluating DES and BMS. This finding has important practical and regulatory implications for future trials investigating the efficacy of new DES and antirestenosis devices.

Author Disclosures

Dr. Pocock has received research grants from Boston Scientific, has received honoraria from Boston Scientific and Conor Medical, and is a consultant/on the advisory board for Boston Scientific. Dr. Lansky has received research grants from Cordis, Boston Scientific, Medtronic, Abbott, and Guidant. Dr. Mehran is on the Speakers' Bureau for The Medicines Company and has received honoraria from The Medicines Company. Dr. Popma has received research grants from Cordis, Medtronic, and Boston Scientific; is on the Speakers' Bureau for Cordis, Boston Scientific, and Medtronic; and is a consultant/on the advisory board for

Cordis, Boston Scientific, and Medtronic. Dr. Dangas has received research grants from Cordis. Dr. Moses has received honoraria and is a consultant to and on the advisory board for Cordis. Dr. Kandzari has received research grants from Cordis, Boston Scientific, and Medtronic; is on the Speakers' Bureau for Medtronic; is a consultant/on the advisory board for Cordis, Boston Scientific, and Medtronic; and is a full-time employee of Cordis Corp. Dr. Ellis has received research grants from Cordis and is a consultant to and on the advisory board for Cordis and Boston Scientific. Dr. Leon has ownership interest in Johnson & Johnson and is a consultant to and on the advisory board for Boston Scientific, Medtronic, and Cordis Johnson & Johnson. Dr. Stone is a consultant to and has received research grants and lecture fees from Boston Scientific Corp., Abbott Vascular Devices, Reva Medical, Xtent, and St. Jude Medical; is on the board of directors for and owns equity in Devax Corp.; and is a past consultant to and has received research grants from Medtronic Corp. and Guidant Corp.

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APPENDIX

For the logistic regression equations relating in-stent LL and in-segment %DS to TLR, please see the online version of this article.

Angiographic Surrogate End Points in Drug-Eluting Stent Trials: A Systematic Evaluation Based on Individual Patient Data From 11 Randomized, Controlled Trials

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